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Hyperbaric Oxygenation (HBO) Clinical Trials: A Review

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HYPERBARIC OXYGENATION (HBO) CLINICAL TRIALS: A REVIEW

By

James Roy Knowles, B.S., M.D.

THESIS

Presented to the Faculty of The University of Texas

Health Science Center at Houston

School of Public Health

in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF PUBLIC HEALTH

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON
SCHOOL OF PUBLIC HEALTH
Houston, Texas
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Dedicated to:

The risen LORD, Jesus Christ,

Who said, "I am the resurrection and the

life; he who believes in ME

shall live even if he dies, and everyone

who lives and believes in ME shall never die."

John 11:25-26.

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I would like to say thank you to my precious wife, Martina, for all her special love and support always. I would also like to thank my children for the special joy they have brought to me.

Submitted: April 20th, 1990

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A REVIEW

James Roy Knowles, B.S., M.D.
The University of Texas
Health Science Center at Houston
School of Public Health, 1990

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Hyperbaric oxygenation (HBO) has been used as a medical intervention for the treatment or prophylaxis of numerous conditions in humans. There is an accumulation of pre-clinical and clinical data supporting its use in humans. It has been asserted that the clinical data are largely derived from anecdotal, uncontrolled observations. The call for reliable data from good clinical trials has sounded forth both from within and from outside the HBO community. A logical question is: "What clinical trials have actually been done to assess the efficacy of HBO, how good were they, and what did they find?" This thesis will present a review of HBO clinical trials which will help answer the above question. The review will identify HBO clinical trials in the general medical literature, assess their methodologic content, and list the reported efficacy of HBO in the various trials. Lastly, the review will briefly discuss its findings as they relate to future clinical research involving the use of HBO.

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INTRODUCTION

> Medicine is an interference with persons. It is tolerated only because the overwhelming balance of its effects is expected to be in patients' interests to bring them benefit rather than harm. The public tolerates medicine only when all reasonable steps are seen to have been taken to guarantee benefit with safety. (Vere, 1976, p. 3)

The basic concepts of hyperbaric oxygenation (HBO) have been used sporadically and in various ways for over 300 years (Fischer, et al, 1988). Current use of hyperbaric oxygenation (HBO) dates from approximately the 1930's when it was used predominantly to treat diving complications - decompression sickness and arterial gas embolism (air embolism), (UHMS, 1989). Circa 1960, HBO began to be used in non-diving clinical applications. Since then, the use of HBO has spread to numerous clinical conditions (Davis and Hunt, 1977, 1988; Fischer, et al, 1988; UHMS, 1989).

There is a fair amount of medical literature worldwide pertaining to HBO. In the only current comprehensive text on HBO therapy, Fischer, et al, cite nearly 1600 references from the world literature regarding the use of HBO (Fischer, et al, 1988). Other HBO texts and reports (Davis and Hunt, 1977, 1988; UHMS, 1989) include additional references, and the Underwater and Hyperbaric Medical Society (UHMS) is in the process of compiling an HBO database which currently has approximately 2300 citations (UHMS, informal communication, 1990). The entire body of HBO literature includes pre-clinical (i.e. basic science, in-vitro, and animal study) data and

clinical (human study) data supporting the use of HBO for various conditions in humans.

Since 1971, more than 87,000 patients in the United States alone have undergone medical intervention (primary or adjunctive) involving the use of HBO for more than 40 different clinical conditions (MIEMSS). No doubt, many more patients have been treated worldwide, as it has been estimated that 85% of all hyperbaric chambers lie outside of the United States (Fischer, et al, 1988).

In this context of worldwide use, with a fair amount of literature and clinical experience, HBO authorities differ in their statements regarding the efficacy of HBO for various conditions. Some believe its use should generally be limited, except for investigational research studies, to 12 indications approved by the Underwater and Hyperbaric Medical Society (UHMS, 1989). Others believe its general use should be for many more conditions (Fischer, et al, 1988).

While there are quite a few proponents advocating the use of HBO for many conditions (Davis and Hunt, 1977, 1988; Fischer, et al, 1988; UHMS, 1989), the assertion has been made that HBO has not been proven clearly efficacious for any condition other than decompression sickness (Robin and Gabb, 1987). In their critical review of HBO, Robin and Gabb stated that HBO is largely an unproven therapy and that its use has been based more on anecdotal reports and theory than upon scientifically-substantiated data such as from well-controlled

clinical trials. Good clinical trials were called for. Respondents to this review included some leading investigators and proponents of HBO. They argued that the review was biased, incomplete, and misleading. That not withstanding, the respondents were unable to effectively refute the assertions (Kindwall, 1988; Goldman, 1988; David, 1988; Robin, 1987, 1988).

The call for better data in the form of good clinical trials has also been sounded from HBO advocates. In the HANDBOOK OF HYPERBARIC OXYGEN THERAPY, Fischer, et al, remarked several times on the need for data from good clinical trials for various conditions (Fischer, et al, 1988, pp. 204, 214, 275).

If more clinical trials are called for, it may be helpful to see what HBO clinical trials have already been done and what they have found. This information may help guide future research, as well as help clarify some of the clinical evidence available regarding the efficacy of HBO as a medical intervention. To the author's knowledge there has not been a formal attempt to assess the methodology of HBO clinical trials, or to summarize their results.

The immediate goal is not to find a definitive answer, such as an exhaustive review might provide, but rather to see what HBO clinical trials the general medical readership likely has had exposure to. It is the general medical literature which provides or should provide the database from which the general medical community will draw conclusions regarding the efficacy of HBO. The potential for HBO to become a generally-accepted

medical intervention depends upon this information and these conclusions. Therefore, the purpose of this study is to answer the question: "According to the general medical literature, what clinical trials have actually been done to assess the efficacy of HBO, how good were they, and what did they find?"

METHODS AND MATERIALS

This study reviews a subset of HBO clinical trials to help answer the above question. The population of interest consists of HBO clinical trials in the general medical literature accessible by MEDLINE. The unit of analysis is each individual report of a HBO clinical trial.

ELIGIBILITY

Inclusion criteria are as follow

1. Studies must meet the definition of clinical trial - "...a prospective study comparing the effect and value of intervention(s) against a control in human subjects." (Friedman, et al, 1985, p. 2)

2. The intervention assessed must meet the definition of HBO or use the term hyperbaric oxygen, and be used either in a primary or adjunctive role. HBO is defined as an intervention in which a patient breathes 100% oxygen intermittently while totally enclosed in a chamber which exposes the patient to pressure in excess of one atmosphere absolute (Fischer, et al, 1988; UHMS, 1989). The intervention may be for therapeutic or prophylactic purposes. Though not strictly meeting the definition of HBO above, studies involving topical HBO (where

only a part of the body is exposed to 100% oxygen and increased pressure) will also be included (Fischer, 1969).

3. The report of clinical trial must be in the English language.

Exclusion criteria are:

1. Studies not meeting the above definition of a clinical trial will be excluded. Specifically, any retrospective study, any study not containing some type of internal control (i.e. studies with external controls such as historic controls or self-controls other than in a crossover design will be excluded), or any study not involving human beings will be excluded.

2. Studies not meeting the above definition of HBO, topical HBO, or not using the term hyperbaric oxygen will be excluded. This definition does not extend to the use of positive pressure breathing or assisted ventilation unless these are administered under hyperbaric conditions in a hyperbaric chamber.

3. Incomplete (abbreviated, interim, or summary) reports of clinical trials will be excluded unless the follow-up or final report is also identified in this review, or the treatment period has been completed and at least a reasonable follow-up period has elapsed.

RECRUITMENT

To identify a subset of HBO clinical trials in the general medical literature, a MEDLINE computer search was accomplished by a medical librarian. The search spanned the years 1965 through 1989. Key terms were hyperbaric oxygen and

(Boolean) clinical trial (and associated clinical trial terms such as controlled, randomized, double-blind, etc.). Reviews in other fields have used a similar method (Mulrow, et al, 1988; Gaul, et al, 1989).

Possible limitations of this method include sampling error and publication bias (Light and Pillemer,1984). Given that this is not intended to be an exhaustive review, but rather a review of a specific subset of HBO clinical trials, neither of these issues are problems for this study.

Citations (and abstracts, when available) of 186 identified articles were obtained from the MEDLINE search. The titles and abstracts were screened to identify reports of HBO clinical trials. Next, 49 potentially relevant articles were pulled. Of these, 28 met the criteria noted above and are included in this review.

DATA COLLECTION

Each of these reports was read and data collected by the author of this review. A data collection instrument constructed for this review was used. This instrument is a form which helps the reviewer secure information from each report regarding the independent variables, and which then allows the reviewer to calculate a methodologic content index (the dependent variable) for each report (see Appendix).

The key elements of the instrument are modifications of a methodologic assessment of medical literature reported by DerSimonian, et al, 1982. In that work, 11 methodologic aspects

of design and analysis of clinical trials were used to assess clinical trials published in four major medical journals. These 11 items were selected

> ... on the basis of their importance to a reader in determining the confidence that should be placed in the author's conclusions, their applicability across a variety of medical-specialty areas, and their ability to be detected by the scientifically literate general medical reader.

These criteria seem especially suited to the review at hand.

For the present review, eight of the items were left unchanged and three were modified slightly to allow greater discrimination of methodologic content. Additionally, rather than the outcomes being "reported, omitted, or unclear" as in the above work, a numeric outcome for each criterion was devised to allow greater discrimination of content by including some features of other published works on quality assessment of clinical trials (Chalmers, et al, 1981; Gardner and Bond, 1990; Bailar and Mosteller, 1988). The numeric valuation also allows the calculation of a methodologic content index (MCI) which is introduced in this review.

In conducting the present review the MCI was initially termed a quality index; however, as was noted by DerSimonian, et al, content does not necessarily guarantee quality. To help make this point clear the name of the index, but not its composition or calculation, was changed.

The independent variables in this study include basic descriptive information of the clinical trial as well as the 11

methodologic criteria. The descriptive information includes seven items: first author, citation, condition treated, type of trial, trial design, reported results, and HBO modality. See figure 1 for these and their possible determinations.

The methodologic criteria are (see figure 2):

1. eligibility criteria for entry of patients into the trial
2. admission (of patients) before allocation (to treatment/control status)
3. random allocation (to treatment/control status)
4. method of randomization
5. patients' blindness to treatment (masking)
6. blind (masked) assessment of outcome
7. treatment complications/possible side effects
8. losses/withdrawals described as to HBO/control status and reason for dropout
9. statistical analyses performed (beyond descriptive statistics such as mean, standard deviation, counts, rates, etc. - e.g. p - values, reports of significance, confidence intervals, etc.)
10. statistical methods (names, details, rationale, etc. of tests used in performing the analyses)
11. power discussed, if no significant difference (between effect of HBO/control) found

The dependent variable is the methodologic content

index (MCI) of each clinical trial. The calculation is similar to that done in the work of Chalmers (Chalmers, et al, 1981). This is computed by summing the total scored on the 11 criteria and dividing this by the sum of total possible. This value is then multiplied by 100 to allow for a 0 - 100 range. Lastly, this number is rounded to the nearest integer. The resultant number is the MCI. This index will be interpreted as the potential quality of a given study. Criteria deemed not applicable for a given trial are not included in the total possible score for that trial (e.g. item 11). See figure 3.

Figure No. 1 HBO Clinical Trial Descriptive Information

1st Author_____

Citation_____

A. Condition_____

B. Type of trial: therapeutic, prophylactic

C. Design: parallel, crossover, other_____

D. Reported results: NS
SS for HBO (5% level)
SS for control

E. HBO modality: Systemic, multiplace
Systemic, monoplace
Topical
Other

Figure No. 2 HBO Clinical Methodologic Criteria

1. Eligibility criteria	0 = not described 1 = partially described (some inclusion or exclusion criteria, but not both) 2 = fully described (both inclusion and exclusion criteria)
2. Admission before allocation	0 = not mentioned 1 = unclear 2 = clearly reported
3. Random allocation	0 = not mentioned 1 = unclear 2 = clearly stated
4. Method of randomization	0 = not mentioned 1 = unclear 2 = clearly stated/or unstated but effectiveness displayed 3 = stated and effectiveness displayed/ tabulated for reader
5. Patient's blindness to treatment	0 = not mentioned 1 = unclear 2 = clearly stated 3 = stated and tested
6. Blind assessment of outcome	0 = not mentioned 1 = unclear 2 = clearly stated
7. Treatment complications/ possible side effects	0 = not mentioned 1 = mentioned, but no active search 2 = mentioned, plus active search

Figure No. 2 (continued)

8. Losses/withdrawals described as to HBO/control status described and reason for dropout	0 = not mentioned 1 = partially 2 = fully described
9. Statistical analyses performed	0 = nothing beyond descriptive information such as counts, means, standard deviations, etc. 1 = unclear 2 = clearly beyond the above
10. Statistical methods	0 = not mentioned 1 = named only/unclear 2 = name, plus details (e.g. rationale, applicability, tailing, etc.)
11. Power discussed, if no significant difference found	0 = not mentioned 1 = unclear 2 = beta specified

Figure No. 3 HBO Clinical Trial Methodologic Index (MCI)

Methodologic Content Index (MCI)

Total scored_____/ Total possible_____ X 100 = _____

N.B. total possible as 24 (22 if criterion number 11 is N/A)

Round score to nearest integer.

DATA PROCESSING & ANALYSIS

One data collection instrument was used per each report of an HBO clinical trial. Simple descriptive statistics (i.e. mean, median, mode, counts, etc.) were calculated with the use of a hand-held statistical calculator. Calculations were repeated three times to ensure accuracy. Given the small number of studies involved and the simple statistics, this seemed adequate. Larger numbers or more complex analyses would require the use of a database and/or statistical software package and a microcomputer.

RESULTS

Reports of 28 HBO clinical trials were assessed in this review. Of these, 26 reported on therapeutic uses of HBO and two reported on prophylactic uses. Reports of 13 trials involved the use of HBO adjunctively with radiation therapy for the treatment of various cancers (tables 1 and 2), six reported on the treatment of multiple sclerosis (MS) (table 3), and two reported on diabetic foot ulcers (table 4). The remaining seven reported on seven different conditions (table 5). HBO was evaluated for a total of 13 different medical conditions, which are listed in table 6.

The earliest publication date was 1972, and the latest was 1989. All but one (Sealy, et al, 1986) of the cancer reports were of studies performed in the 1970's. Reports published in the 1980's were generally more methodologically completed than in the 1970's, though there were notable

exceptions in both decades (Thurston, et al, 1973; Baroni, et al, 1987; Esterhai, et al, 1987; - scores 70, 27, 25 - see tables 4, 3, and 4 respectively).

Methodologic content varied quite a bit between studies. The lowest score was 18 and the highest was 88 (0 to 100 possible). Table 7 shows the distribution of MCI scores as a stem and leaf plot. The mean, median, and mode are shown in table 8. High scores, as noted above, tended to be in more recent studies. There was a clustering of very high scores in the MS reports, which were the only double-blind designs (see table 3). The highest scored (Harpur, et al, 1986) trial was also in the MS group and was the only trial which actually tested patient blindness/masking to ensure its effectiveness.

The prevalence (sic) of highest scores for each of the 11 methodologic criteria is presented in table 9. Ideally, a population of methodologically complete clinical trials (as judged/defined by these criteria) would have close to a 100% prevalence of these highest scores for each criterion. Continuing with this analogy (prevalence of methodologic completeness), this review population of HBO clinical trials has a relatively high prevalence of full eligibility (85.7%), statistical analyses beyond means, etc. (85.7%), and random allocation (stated but not described) (82.1%).

This population has a low prevalence of tested patient blindness/masking to treatment (3.7%), specification of power in the presence of the finding of a non-significant difference

(16.7%), and patient blindness/masking to treatment (even when not tested) (18.5%). From an absolute rather than relative perspective, perhaps all prevalences below a given value or acceptable standard (e.g. 80%) should be considered low. In this case items 2, 4-8, 10 and 11 could be considered methodologic deficiencies as a whole for this population.

The reported efficacy of HBO in these trials for the various conditions is shown in tables 1-5. A rather mixed review is evident, with a few significant findings, but no consistently positive pattern. On the contrary, the 5:1 ratio of NS to SSH findings in the high-scoring group of MS trials is convincing that HBO was not effective for MS.

The diabetic foot ulcer trials are difficult to compare. They used different HBO modalities, on wounds probably at different ends of the clinical spectrum, and had marked differences in their MCI's.

The cancer trials show generally negative results, though none of these studies really answered the question of power. The cancer trials seem to be an historical note at this point - a veritable flurry of clinical trials in the 70's to see if HBO showed worthwhile benefit.

The assorted conditions also show a mixed review of findings as well as methodologic content. The most notable in this group is the recent high-scoring trial for carbon monoxide poisoning (Raphael, et al, 1989). With the high power set at the beginning of the study (the only study to do this, as

opposed to post hoc analysis done in two others) and the large numbers and overall content of the study it draws a strong conclusion which is at odds with prevailing opinion of HBO proponents (Fischer, et al, 1988; UHMS, 1989).

Another report worth noting is the myocardial infarction (MI) study (Thurston, et al, 1973). It was a well-designed trial with a potentially very worthwhile finding - see table 5. No other MI studies were identified in this review.

Overall, in this review, the efficacy of HBO in clinical trials could be classified as: not effective in MS; probably not effective in CO poisoning; possibly effective in acute acoustic trauma; equivocal as an adjunct with radiation therapy in various cancers; questionable in diabetic foot ulcers; and investigational in the other conditions. Relatively low MCI's and small numbers of trials per condition make it difficult to be firm about any condition other than MS.

Table 1. Format For All Tables Listing HBO Clinical Trials By Condition.

Clinical trials by condition

First author	Year published	Methodologic Content Index (MCI) (0 - 100)	Reported findings (for one or more endpoints)
			NS = not significant at 5% level
			SSH = statistically significant for HBO
			SSC = statistically significant for control

Table 2. HBO Clinical Trials: Cancer (All Adjunctive With Radiation Therapy)

BLADDER CANCER			
Plenk	1972	59	SSH (comparison of survival curves, but not overall survival at any given point)
Dische	1973	50	NS
Cade	1978	42	NS
CERVIX CANCER			
Fletcher	1977	46	NS
Watson	1978	50	SSH (local tumor control, but not overall survival)
Ward	1979	50	NS
GLIOBLASTOMA			
Chang	1977	21	NS
HEAD & NECK CANCER			
Chang	1973	54	NS (lack of power implied)
Sealy	1977	29	NS (lack of power implied)
Berry	1979	59	SSH (local tumor control and 5 yr survival)
Sause	1979	46	NS (lack of power implied)
Sealy (used with misonidazole as a penetrating agent)	1986	67	NS
Henk	1986	59	SSH (local tumor control and 5 yr survival)

Table 3. HBO Clinical Trials: Multiple Sclerosis

MULTIPLE SCLEROSIS				
*Fischer	1983	82	SSH	(objective improvement, was mostly transient)
*Neiman	1985	79	NS	(lack of power implied)
*Wood	1985	75	NS	
*Harpur	1986	88**	NS	(power was greater than 90-95% for all but one endpoint)
*Wiles	1986	83	NS	(power was 90%)
*Barnes	1987	71	NS	

*indicates double-blind trials (the only such trials in this review)
**only study which tested patient blinding

Table 4. HBO Clinical Trials: Diabetic Foot Ulcers

DIABETIC FOOT ULCERS				
Baroni (gangrenous)	1987	27	SSH	(SS for rate of amputations; NS for wound size)
**Leslie (Non-gangrenous)	1988	71	NS	(only wound size assessed)

**indicates topical HBO was used (this was the only clinical trial to use this modality)

Table 5. HBO Clinical Trials: Assorted Conditions

ACOUSTIC TRAUMA				
Pilgramm	1985	55	SSH	
CARBON MONOXIDE POISONING (CO)				
Raphael	1989	79	NS	(power was 95% for patients with no or only brief loss of consc.; lacked power to assess efficacy in patients with coma)
HEAD TRAUMA				
Artru	1976	58	NS	
MYOCARDIAL INFARCTION (MI)				
Thurston	1973	70	SSH	(reduced risk of mortality in patients with prognosis other than "good")
OSTEOMYELITIS (chronic refractory)				
Esterhai	1987	25	NS	
*HEPATITIS (prevention of halothane-induced subclinical hepatitis)				
Pratilas	1978	18	SSH	
*OSTEORADIONECROSIS OF THE MANDIBLE (prevention of, as compared to penicillin, in patients at risk)				
Marx	1985	36	SSH	

* = the only prophylactic trials identified in this review

Table 6. HBO Clinical Trials: Summary of Conditions

Conditions (1-11, therapeutic; 12-13, prophylactic)

1. acoustic trauma
2. bladder (2-5 are cancers - all in conjunction with radiation therapy)
3. cervix
4. glioblastoma
5. head and neck
6. carbon monoxide poisoning (CO)
7. diabetic foot ulcers

Table 6 (continued)

8. head trauma (presenting in coma)
9. multiple sclerosis (MS)
10. myocardial infarction (MI)
11. osteomyelitis (chronic refractory)
12. hepatotoxicity (subclinical) due to halothane anesthetic
13. osteoradionecrosis of the mandible

Table 7. HBO Clinical Trials: Stem and Leaf Plot of MCI Scores

```
8)2 3 8
7)0 1 1 5 9 9
6)7
5)0 0 0 4 5 8 9 9 9
4)2 6 6
3)6
2)1 5 7 9
1)8
```

Table 8. HBO Clinical Trials: Descriptive Statistics of MCI Scores

Range of methodologic content: 18 - 88

Median = 54.5

Mode = 50, 59

Mean = 55.3

Std dev (n-1) = 19.9

Table 9. HBO Clinical Trials: Prevalence of Highest Methodologic Criteria Scores.

1.	Full eligibility criteria	24/28	85.7%
2.	Admission to trial clearly before allocation to HBO/control groups	13/28	46.4%
3.	Random allocation clearly stated	23/28	82.1%
4.	Method of randomization clearly stated and its effectiveness displayed/tabulated for reader	9/28	32.1%
*5.	Patient's blindness to treatment clearly stated and tested in the trial	1/27** 5/27	3.7% 18.5% (not tested)
*6.	Blind assessment of outcome clearly stated	6/26***	23.1%
7.	Treatment complications/ possible side effects mentioned plus an active search for them	7/28	25.0%
8.	Losses/withdrawals fully described as to HBO/control status and reason for dropout	10/28	35.7%
9.	Statistical analyses clearly beyond descriptive information (i.e. beyond mean, SD, etc.)	24/28	85.7%
10.	Statistical methods described beyond name (i.e. rationale, applicability, tailing, etc.)	6/28	21.4%
11.	Power or beta specified, if no significant difference found.	3/18****	16.7%

* = only the MS studies met these criteria
** = in one trial this criterion was judged N/A due to all patients being in coma during all treatments
*** = in two trials this criterion was judged N/A - in one the only endpoint was mortality, in the other the only endpoints were regaining consciousness and mortality.
**** = in ten trials this criterion was judged N/A because a significant difference was found in one or more endpoints

DISCUSSION

Strong but differing opinions exist regarding the efficacy of HBO for various clinical conditions (Davis and Hunt, 1977, 1988; UHMS, 1989; Robin and Gabb, 1987; Robin, 1988; Fischer, et al, 1988). The issue is, how is the truth best discovered as it relates to medical interventions in general and to HBO specifically?

Are clinical trials always needed to evaluate a medical intervention? No. When a new or unproven medical intervention results in a dramatic or marked effect (for example a drop in case-fatality rate from 90% to 50%) as compared to the best available current therapy for a given condition, the "traditional" or historic control (comparison of a number of treatment cases with general clinical experience) approach may provide acceptable evidence for the efficacy of the intervention in question (Lilienfeld, 1976). Examples of this include the sharp reduction of the case-fatality rate due to the use of penicillin for certain infectious diseases (Lilienfeld and Liliendeld, 1980), or the use of streptomycin for tuberculous meningitis (Bulpitt, 1983).

When are clinical trials needed? When a new or unproven medical intervention results in less than clear-cut dramatic results, more than simple case series compared against historical controls are needed.

> When a new treatment results in small improvements in the course of a disease, or a large number of known and/or unknown factors influence the outcome of the

> disease, it is necessary to conduct a well-planned controlled study in an explicitly defined group where the treatment(s) or absence of treatment (control) can be allocated to subgroups in a systematic manner. (Lilienfeld and Lilienfeld, 1980, p. 262)

The well-designed and executed clinical trial is the best such controlled study, because it uses the scientific method of experimental design. This design has the strongest inferential value of all study designs (Vere, 1976; Ibrahim, 1985). "A clinical trial is the most definitive method of determining whether an intervention has the postulated effect." (Friedman, et al, 1985, p. 3)

What if clinical trials are performed, but not well-designed or well-executed? Simply the performance of clinical trials is not enough; the trials must be of good quality. Mosteller, et al, cite two long-term problems, and imply a third, resulting from the performance and publication of "weak" clinical trials. First, it may result in the delay or omission of good "strong" trials. Second, in may facilitate the continued use of accepted, but ineffective interventions. Third, it may result in excessive human suffering and economic costs due to pursuing ineffective or less effective interventions (Mosteller, Gilbert, and McPeek, 1983).

The need for good clinical trials in HBO is highlighted by the findings in one of the trials in this review - the study by Raphael, et al, 1989. The efficacy of HBO over normobaric oxygen for CO poisoning has been stated with certainty by HBO

proponents (Fischer, et al, 1988; UHMS, 1989). The negative finding of a fairly methodogically complete study with high power seems difficult to refute. It also shows how different the truth may be from some strongly held perceptions, thus emphasizing the need for good data derived from good clinical trials. (Of note, the perceptions of usage of HBO for CO poisoning have also recently been challenged - Roy, et al, 1989.)

Good clinical trials may be a bitter pill for HBO; a kill or cure remedy. Without them HBO will likely fall into disrepute and disuse (except probably for decompression sickness, DCS) simply from the lack of proof in light of a challenge. With good clinical trials it runs the risk of a rapid fall-off in usage if findings are negative. If the clinical trials result in a clearly positive finding for any indication, a useful medical intervention will have been salvaged. In their review, Robin and Gabb, 1987, noted that DCS was the only use of HBO for which "...proof of efficacy has been established...", citing "...extensive clinical experience...", including "...some elements of alternating single-patient clinical trials." No clinical trials involving DCS were identified in this present review.

Is one good clinical trial enough to determine the efficacy of HBO for a given condition? Probably not. (Thus the caveat with the above CO study.) For example Fischer, et al, 1983, were the first to publish an HBO clinical trial for MS.

The results were positive. In contrast, five subsequent trials (all of comparable quality) were negative. One might suspect that with an alpha level of .05 for most clinical trials one trial out of 20 may result in a false positive finding simply by chance. To ensure accuracy and consistency, it seems best to draw conclusions from more than one good clinical trial.

The value of judging the quality of a clinical trial is evident. One reason is it helps the reader decide how much credence to place in the results/findings of a given trial. For example, a recent clinical epidemiology text advises physicians to disregard any clinical trials which are not randomized (Sackett, et al, 1985). The authors think that randomization is such a strong quality indicator by itself that its absence should bar a clinical trial from serious consideration by the general medical reader.

Another benefit of quality assessment is that it allows one to sort-out and make better sense of conflicting results of different clinical trials. If one can demonstrate a significant qualitative difference between studies with differing results, then credence may be place in high quality findings which are consistent with each other.

A third benefit of quality assessment is in guiding future research. If results are clearly conflicting among high quality studies this may highlight a key area for research to clarify the reasons for the different outcomes (Light and Pillemer, 1984). Also, as medical research presses on from the

unknown to the known, identification of good and bad clinical trials helps to accurately map the known and unknown areas. This helps prevent redundancy, inefficiency and the three problems cited earlier.

Clinical trial assessment schemes range from simple to complex, with varying amounts of emphasis on different elements and considerations in clinical trials (Chalmers, et al, 1981; Bailar and Mosteller, 1988; DerSimonian, et al, 1982; Bulpitt, 1983). The assessment involves evaluation of methodological content and quality.

There are many books which discuss clinical trials and serve as sources to help physicians and others design, execute, and analyze clinical trials (Shapiro and Louis, 1983; Friedman, et al, 1985; Bulpitt, 1983; Good, 1976; Tygstrup, et al, 1982). While there has been no such thing as a perfect trial in practice, the fact that there is the concept of an ideal trial, which serves as the target, keeps fostering the improvement of actual trials (Friedman, et al, 1985; Bailar, 1983). Detailed discussion of the elements of clinical trials is beyond the scope of this review - the interested reader is referred to the above sources.

Content potentiates or facilitates quality. A clinical trial with most of the essential methodologic elements (e.g. randomization, blinding/masking, statistical analysis, etc.) has the potential to be a very good study, but quality is not guaranteed.

The corollary is that quality is based on or requires content. A clinical trial with few or none of the essential elements of a good trial has essentially no chance of being a good clinical trial.

An example of the difference between content and quality is clearly seen regarding the element of statistical tests or methods. Content asks the question, "Were the tests/methods stated?" Quality asks the question, "Were the tests/methods appropriate and correctly applied?"

Reviewing an article for content is much easier, but less accurate than reviewing it for quality. Conversely, reviewing an article for quality is more accurate, but more time-consuming (the quality assessment instrument designed by Chalmers, et al, 1981, is a good example). Also, reviewing for quality requires the reviewer to have more expertise in statistics as well as the clinical area being reviewed.

In this review I chose to assess content because this seemed to be a good "coarse" screening tool - able to quickly identify the potentially good studies and the almost certainly bad studies. From this point, one could do "fine" screening/evaluation of selected high MCI studies with a good quality assessment tool. In a sense, the content review (MCI) could be the "inexpensive" (easier to perform, requiring less expertise) high sensitivity screening test. The quality review could be the "expensive" (harder to perform, requiring more expertise) high specificity - and, in this case, high

sensitivity as well - confirmatory test to detect good clinical trials.

The data collection form used in this review needs to be validated. One step toward validation would be to have several reviewers use the instrument for the review, then assess problems that arise as well as variability between reviewers. Another step would be to review the UHMS database, then submit the results of the review to critical assessment by others.

Once the instrument is validated it could be used to perform an exhaustive review of all HBO clinical trials worldwide. This would be particularly valuable in the field of HBO, as it has become a globally-utilized intervention and a significant proportion of research is done in other countries (such as the Soviet Union) and published in other languages (Fischer, et al, 1988). A quick content review followed by a more detailed quality review on the high MCI trials would help clarify the proper use of HBO as well as guide further research.

CONCLUSIONS AND RECOMMENDATIONS

This review has characterized the HBO clinical trials published in the general medical literature (accessible by MEDLINE) from 1965 through 1989. The methodologic content of the trials was assessed and the reported efficacy of HBO from the trials was listed and summarized. The methodologic content has been emphasized as an indicator of the potential quality of a given clinical trial. A methodologic content index (MCI) was introduced in this review and its need for validation was

discussed. The value of performing quality assessment on selected high MCI studies was discussed.

There have been some methodologically sound clinical trials performed as well as some unsound studies to assess HBO. This review indicates that the only clinical condition which has been studied sufficiently to draw firm conclusions about HBO's efficacy is multiple sclerosis. According to this review the general medical readership could conclude that HBO does not appear to be efficacious for MS. Evidence is inconclusive for other conditions - due to relatively unsound studies and/or small numbers (often single) of studies per clinical condition (narrow inferential base). The only possible exception is a recent carbon monoxide study which found HBO was not better than normobaric oxygen.

The fact that some good clinical trials were done helps set the stage for more to be done in the future. Areas specifically needing the most improvement are: patient blinding/masking to treatment as well as the assessment of that blinding in the trial, and attention to the power of the trial. The need for further good clinical trials is stressed. A more comprehensive review of HBO clinical trials is recommended.

APPENDIX

HBO Clinical Trial Methodology Review Form

Article No. _____ Reviewer _____

1st Author _____

Citation _____

A. Condition _____

B. Type of trial: therapeutic, prophylactic

C. Design: parallel, crossover, other _____

D. Reported results: NS
SS for HBO (5% level)
SS for control

E. HBO modality: Systemic, multiplace
Systemic, monoplace
Topical
Other

1. Eligibility criteria
   0 = not described
   1 = partially described (some inclusion or exclusion criteria, but not both)
   2 = fully described (both inclusion and exclusion criteria)

2. Admission before allocation
   0 = not mentioned
   1 = unclear
   2 = clearly reported

3. Random allocation
   0 = not mentioned
   1 = unclear
   2 = clearly stated

4. Method of randomization
   0 = not mentioned
   1 = unclear
   2 = clearly stated/or unstated but effectiveness displayed

APPENDIX (continued)

		3 = stated and effectiveness displayed/tabulated for reader
5.	Patients' blindness to treatment	0 = not mentioned 1 = unclear 2 = clearly stated 3 = stated and tested
6.	Blind assessment of outcome	0 = not mentioned 1 = unclear 2 = clearly stated
7.	Treatment complications/ possible side effects	0 = not mentioned 1 = mentioned, but no active search 2 = mentioned, plus active search
8.	Losses/withdrawals described as to HBO/control status and reason for dropout	0 = not mentioned 1 = partially described 2 = fully described
9.	Statistical analyses performed	0 = nothing beyond descriptive information such as counts, means, standard deviations, etc. 1 = unclear 2 = clearly beyond the above
10.	Statistical methods	0 = not mentioned 1 = named only/unclear 2 = name, plus details (e.g. rationale, applicability, tailing, etc.)
(11.)	Power discussed, if no significant difference found	0 = not mentioned 1 = unclear 2 = beta specified

APPENDIX (continued)

Methodologic Content Index (MCI)

Total scored_____ / Total possible_____ x 100 = _____

N.B. total possible is 24 (22 if criterion number 11 is N/A)

Round score to nearest integer.

Comments/questions/problems:

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